Schizophrenia Bulletin vol. 34 no. 2 pp. 253–255, 2008
doi:10.1093/schbul/sbm151
Advance Access publication on January 18, 2008

What Did the WHO Studies Really Find?

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The article by Cohen et al.[1] raises important issues and provides a useful synopsis of published studies on schizophrenia outcomes in 11 low- and middle-income countries. The authors use this material to challenge what they claim to be an ''axiom'' (ie, a self-evident proposition requiring no proof) of better course and outcome in developing countries which has been ''embraced'' by international psychiatry. They impute the origin of this belief primarily to World Health Organization (WHO)–led international collaborative research conducted over the past 30 years[2–5] and caution that the publication of the final report from the International Study of Schizophrenia (ISoS)[6] might even further bolster convictions in the ''better prognosis'' hypothesis. Based on evidence from research conducted outside the WHO studies, they conduct a reexamination of the axiom.

Having been directly involved with the WHO schizophrenia research program over decades, we wish to point out that Cohen et al[1] have misunderstood key aspects of the design and conclusions of the WHO studies. They claim that ''the sampling methods utilized in the WHO studies may have resulted in overly optimistic perceptions of course and outcome'' because ''case-finding methods which focus exclusively on help-seeking agencies will miss large proportions of seriously ill, poor prognosis individuals.'' They state, mistakenly, that the WHO studies provide no evidence allowing an evaluation of ''the quality of family and social interactions,'' and impute to them by implicating a view that ''scarcity'' of care resources is responsible for better outcomes. Because these claims repeat an earlier critique of the WHO 10-country study (Determinants of Outcome of Severe Mental Disorders [DOSMeD][4]) by Edgerton and Cohen in 1994,[7] which was answered by us in a publication[8] not quoted in the present article, we summarize briefly the relevant features, findings, and conclusions of that study.

An unexpected finding of the follow-up stage of the WHO International Pilot Study of Schizophrenia (IPSS)[3] was a markedly better overall outcome of schizophrenia patients in India and Nigeria at 2-year and 5-year follow-up. Because the IPSS cohort was not necessarily representative and the finding could be an artifact of selection, a second, epidemiologically designed study was launched in the early 1980s. DOSMeD[4] was the first large-scale study in which a unified design, stringent methods, and standardized instruments were concurrently applied to first-episode *incident* cohorts (total study population = 1379) at 12 research sites in diverse sociocultural settings (Colombia, Czechoslovakia, Denmark, India, Ireland, Japan, Nigeria, Russia, United Kingdom, and United States). The cohorts were recruited by 2-year *active* case finding within defined geographical areas, aiming to intercept *all* new onsets at all kind of facilities—not just mental health services, but including primary care, police/prisons, traditional healers, and religious shrines (notably, 28% of the cases in India and Nigeria were recruited through such ''alternative'' care sources). For 86% of the cases, the duration of untreated psychosis was less than 1 year, and only 10% had been prescribed antipsychotic drugs prior to entry into the study. Repeated ''leakage'' checks on the completeness of case finding found that only a handful of incident cases had been missed by this technique, thus categorically ruling out an ascertainment bias favoring inclusion of milder or good prognosis cases. Patients and key informants were interviewed at baseline and at 1-year and 2-year follow-up (78.2% of the cohort), and a large proportion of the original cohort was traced and assessed again at 15 years (as part of the ISoS[6]) in 8 of the 12 field research centers. Throughout the study, high intra- and intercenter reliability of assessment using the Present State Examination (PSE)[9] was maintained by joint rating of live and prerecorded interviews. Diagnostic stringency was ensured by processing of the PSE data using a computerized diagnostic algorithm.[9] During the first 2 years, nested studies were conducted on the impact of potential precipitants of psychotic relapse: stressful life events[10] (in 10 of the centers) and expressed emotion[11] (in Chandigarh, India). These studies did provide important information on family and social interactions. Operationally defined measures of course and outcome included 1 categorical

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index (pattern of course) and 6 quantitative dimensions (cumulative percentages): estimated follow-up time in psychotic episodes, in complete or incomplete remissions, duration of unimpaired community functioning, time in hospital, and time on antipsychotic medication. In all centers, disability and social functioning were evaluated using the WHO-Disability Assessment Schedule interview. Importantly, our analysis did not conflate measures of clinical status and measures of social functioning. Analysis of predictors of outcome was based on log-linear models (log-odds) which tested 25 potential predictors against the 7 outcome variables.

The essence of the findings and conclusions of the study are best conveyed by quoting from the DOSMeD final report.[4] The study demonstrated clearly a diversity of outcomes but "did not identify any particular pattern in the course and outcome of schizophrenic illnesses which could be regarded as specific to a given area or culture." The outcome of patients in the developing countries was not *uniformly* better, as compared to the outcome in developed countries. While high rates of complete clinical remission were significantly more common in developing country areas (37%) than in developed countries (15.5%), the proportions of continuous unremitting illness (11.1% and 17.4%) did not differ significantly across the 2 types of setting. Patients in developing countries experienced significantly longer periods of unimpaired functioning in the community, although only 16% of them were on continuous antipsychotic medication (compared with 61% in the developed countries). Across all centers, the best predictors ($P < .001$) of outcome were type of onset (insidious vs acute) and type of setting (developed vs developing country), followed by marital status ($P < .01$) gender ($P < .05$), social isolation ($P < .05$), and drug abuse ($P < .05$). Neither type of family household (extended vs nuclear) nor experienced avoidance by others (a putative marker of stigma) reached statistical significance as predictor of outcome.

Having excluded a number of potential confounders, we concluded that "it is unlikely that the variation in course and outcome could be reduced to a single variable" and considered "the possibility that the clinical conditions meeting the inclusion criteria of the study in the 2 types of setting may be heterogeneous and include varying proportions of etiologically and genetically different disorders which may be indistinguishable from one another at the level of the phenotype…This possibility exists but it cannot be properly examined or tested at the present time, in the absence of established genetic markers, indicators of etiology, or other underlying mechanisms of disease." Nevertheless, "a strong case can be made for a real pervasive influence of a powerful factor which can be referred to as "culture," as the context in which gene-environment interactions shape the clinical picture of human disease…The contribution of the present study is not in providing the answer but in clearly demonstrating the existence of the question."[4]

Cohen et al[1] cite and review a number of non-WHO studies in low- and middle-income countries as providing evidence that is contrary to the "presumed wisdom" allegedly promoted by the WHO reports. Yet they note the "heterogeneity in types of samples, follow-up periods, and outcome measures" used in those studies, acknowledge that no meta-analyses were possible, and base their reasoning on "reading of the research reports, tabulations of the available data, and interpretations of the evidence." Using the same method in our perusal of Tables 3 and 5 in the target article, we are unable to find in this literature evidence contradicting any of the DOSMeD and ISoS findings and conclusions. In fact, notwithstanding the heterogeneity of the data due to design, methods, and power, nearly all studies report extraordinarily high proportions of "complete recovery," "no or minimal psychotic symptoms," "no psychotic episodes," "no impairment," "good to excellent social functioning," etc. We agree that mortality is an important measure of outcome and that wherever standardized mortality ratios (SMRs) are available, people with schizophrenia tend to have elevated rates, compared with the general population. In the ISoS study,[5] SMRs were calculated for 6 schizophrenia cohorts in developing countries and 12 cohorts in developed countries. Of the 13 SMR values significant at $P < .05$, 4 were in developing countries and 9 in developed countries. All the 5 highest values (SMR > 4.0) were in developed countries. Had Cohen et al[1] included in their review comparable data from course and outcome studies in high-income countries, the contrast between the 2 groups of settings would be striking.

We do not argue that the prognosis of schizophrenia in developing countries is groupwise uniformly milder or that the existing huge gaps in mental health service provision between high- and low-income countries are irrelevant to the lives of millions of people affected by this disorder. On the contrary, the erosion of social support systems, likely to be associated with the processes of globalization,[12] should be a matter of grave concern. The sobering experience of high rates of chronic disability and dependency associated with schizophrenia in high-income countries, despite access to costly biomedical treatment, suggests that something essential to recovery is missing in the social fabric. Thus, the existence of outcome differentials between populations and cultures is not "presumed wisdom" but a real complex issue which should be addressed with standards of precision and rigor that are customary in scientific research and discourse.

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